nance diet" of only 1000 to 1200 calories were some in which diet had been broken so that treatment was not complete at discharge, though they were not more severe than some others. It is recognized that in cases more severe than these the standard of treatment mentioned sometimes necessitates extreme emaciation and weakness if the attempt is to be made to prevent downward progress by keeping the diet strictly within the assimilative power. These distressing end-stages may be either prevented or postponed by application of the same principle in the earlier stages, and for this purpose it will be noted that the diet in even the mildest cases was fixed so as to maintain a reduced level of weight.

PROGNOSIS. Notwithstanding the general favorable progress in hospital the prognosis is recorded as unfavorable in a high proportion of the cases. It unfortunately is still unproved whether the best treatment by the present methods can succeed permanently in arresting the downward progress in severe cases. But when poorly educated patients must go out to make their living in unfavorable environment without proper supervision, the result can be easily foretold. Unsuccessful attempts were made to interest the Red Cross and other organizations in establishing some institution or colony for the after-care of such patients, whose fate is typical of the neglect of chronic disease among the poorer classes in most communities.

STUDIES IN BONE GROWTH: AN EXPERIMENTAL ATTEMPT TO PRODUCE PSEUDARTHROSIS.

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ASSISTED BY

HAROLD F. MORRISON, FIRST LIEUT., M.C., U.S.A.

THE studies herewith presented, and others which will be published later, were made possible through the generosity of the Surgeon-General in permitting the addition of a well equipped animal research annex to the pathological laboratories at U. S. Army General Hospital No. 3, Colonia, N. J., thereby affording facilities for the continuation of investigations relative to bone growth and allied subjects.

In the early months of our participation in the War, during the preliminary organization of this hospital under the joint auspices of the Red Cross and the Surgeon-General's Office, the author, who had been designated as director of the hospital, was allowed to draw the plans of the laboratories to include not only the usual pathological and bacteriological departments, but a completely equipped animal research annex. As a result of a conference with Colonel F. F. Russell, M.C., Chief of the division of laboratories, privileges were granted which anticipated the work included in this paper by making ample provisions for further research in bone metabolism.

U. S. Army General Hospital No. 3 was opened for the treatment of surgical cases in the summer of 1918, the first patients being admitted early in July, 1918. En passant, it is of interest to note that of all the hospital units whose preliminary organization was made under the Red Cross, in conjunction with the Surgeon-General, this institution was the only one to be ultimately established as a military hospital in this country.

The laboratory, as planned at U. S. Army General Hospital No. 3, included animal houses, animal operating-room and animal autopsy-room, as well as the usual departments of the clinical sections of the laboratory, namely, large chemical, bacteriological and pathological rooms. Coincidently with our clinical bone work, research in various allied problems was made since the early days of the hospital's establishment. These experimental studies were carried on under the auspices of the Surgical Service, with the close and efficient coöperation of the laboratory staff.

Such resources in equipment and technical assistance permitted the continuation of investigations especially desired by the author; foremost among which were an experimental study of the etiology of pseudarthrosis and an attempt to discover some trustworthy artificial stimulus to osteogenesis. This research was carried on with the object of supplementing earlier investigations,[1] made about ten years ago at the Cornell Animal Hospital, which dealt with various phases of bone growth, such as the experimental fusing of dogs' vertebræ by means of the inlay graft, and studies of the relative osteogenesis of bone obtained from various portions of dogs' and rabbits' anatomy. It was found at that time that cubes of bone removed from the spinous process of a vertebra were much less active osteogenetically when placed in a muscle belly, than were cubes of the same size taken from the shaft of a dog's long bone, thus proving the advisability of employing the bone graft for fusing the vertebræ in such conditions as caries of the spine, compression fractures of the vertebral bodies, selected cases of scoliosis, et cetera.[2]

Other experimental investigations were made at that time concerning the relative osteogenetic properties of the periosteum when secured by *scraping the outer surface of the bone* with a sharp instrument, as compared with the osteogenetic power of the outer portion of the periosteum when obtained by means of *separation through the easier line of cleavage* with the use of a blunt instrument. In the first instance, the *complete* periosteum was obtained, and this was found to be a very potent osteogenetic element, whereas, in the latter case, osteogenetic activity was found to be only localized in those spots where portions of the cambium layer (which, alone, contains the active bone-growing cells) happened to come away with the so-called "limiting membrane" of Macewen. Studies were also continued which bore out the inadvisability of attempting the transplantation of bone tissue from one species to another, such as the grafting of sheep's bone into a dog, or dog's tissue into a rabbit. These latter findings, it is believed, bear very materially upon the ruling out of any attempts to transplant animal bone into the human subject and the advisability of always using, when possible, autogenous graft material.

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[1] Albee, F. H.: An Experimental Study of Bone Growth and the Spinal Transplant, Jour. Am. Med. Assn., 1913, lx, 1044–1049.

[2] The lowered osteogenetic potency of the spinous processes of the vertebræ, largely due to their meagre periosteum and excess of ligamentous attachments, was clearly demonstrated by these experiments. Therefore, in attempting fusion of the vertebræ, it is more trustworthy to inlay a bone graft which thus supplies the needed osteogenetic activity at the same time that internal fixation is produced.

Our bone research work at U. S. Army General Hospital No. 3 included an experimental study of pseudarthrosis, with a special object of determining the influence, if any, exerted by the roentgen ray upon callus formation. Another purpose of our investigations was to discover some trustworthy artificial stimulus to osteogenesis. A report of these latter findings will be published by the author at an early date.

The first experimentations at this hospital were carried on in an endeavor to ascertain, if possible, the etiological factor in pseudarthrosis, or malunion. One has but to observe the vast amount of literature written on the subject to realize the surgical importance of this condition. Whether the ever widening interest in this unfortunate malady is indicative of an actual increase in its prevalence, under our modern methods of living, is open to debate. The experience of the author, during the past fifteen years, would certainly bear out the impression that pseudarthrosis is on the increase. This conclusion has been strengthened by discussion with many colleagues likewise interested in bone work. In this connection, a Canadian surgeon recently assured the author that, in his opinion, change of diet necessitated by the Great War was the cause of the very large increase in such cases in his own practice. Among the many factors[3] to which has been attributed a possible role in the causation of pseudarthrosis, special attention has been given to the following:

1. *Method of Splinting.* A consideration of influences possibly favoring the production of pseudarthrosis has included the type of splint and its adjustment in relation to interference with normal circulation; the length of time that the splint should be worn; the proper time for instituting massage; the type of coaptation splints; and the value of traction.

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[3] In passing wholly from clinical experience, it is the opinion of the author that syphilis has been greatly overestimated as a cause of this condition.

2. *Diet.* As referred to above, diet has frequently been discussed as a possible cause, in its relation to sluggish bone growth.

3. *Location of the nutrient artery,* with respect to the fracture, and the possible interference therefrom with the blood supply to the region of the fracture.

4. *Presence of Systemic Disease.* Lues, or atrophic conditions, such as neuro-arthropathies, etc., have been considered, in their influence upon bone metabolism.

5. *The Internal Application of the Metal Plate.* From the author's clinical experience, this would appear to be one of the most frequent causes of pseudarthrosis. In this hospital, there have been a goodly number of cases of malunion, without loss of bone substance, all of which have occurred in young soldiers, averaging unusual good health. In a large percentage of these cases, metal plates had been previously applied.

6. *The Roentgen Ray.* It is an established fact that repeated massive exposure to the roentgen ray is a potent inhibitor to cellular growth, in reference to spermatozoa, etc.

Of all the influences enumerated above, that of the roentgen ray is the only one which has been markedly increased within the last decade. In a modern bone clinic, it is, indeed, a rare exception when a fracture is not subjected many times to radiographic examination. The remarkable increase in prevalence of pseudarthrosis coincident with the coming into common usage of the roentgen ray presents a possible correlation. In a consideration of factors contributing to the causation of pseudarthrosis, it seemed, therefore, to the author that the influence of the roentgen ray should be one of the first to be investigated.

In our studies in bone growth, rabbits were selected as the experimental subjects. Young to middle-aged adults were chosen, no animals of either age-extreme being used. Careful asepsis was invariably observed, the field of operation being always treated with a 3½ per cent. tr. iodin preparation. In our entire series of cases, numbering over 80, together with controls, there were but 2 instances of infection. These both occurred in the earlier studies in pseudarthrosis, and were in cases of compound fracture of both bones of the foreleg.

In the majority of our early experiments, it was our method to fracture both bones of the foreleg, an external splint being then applied for fixation and support. The numerous contrivances which are employed for such purposes vary widely in efficacy and cost.[4]

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[4] While studying methods of rehabilitation in Canada, the author was especially impressed with one type of splint that was shown him at a certain institution. It was a rather complicated, hinged device, of aluminum, consisting of several parts riveted together, and was manufactured at that hospital in a shop specially organized for the purpose.

The contrast, in cost of material and of manufacture, between this splint and one about to be described is worthy of consideration.

In an attempt to secure an adequate splint for the rabbit's leg, one that would at once maintain immobilization of the fractured fragments, as well as prevent the animal from gnawing its foot, the following extremely simple method was devised of producing an efficient splint:

A piece of copper wire mosquito-netting, 3″ x 6″, is placed on a pine board with the center of the netting square directly over a hole, $\frac{5}{8}$ inch in diameter, through which by means of a blunt soft pine plug, the netting is driven by a mallet and moulded into a cylinder, one end of which is closed. By trimming with the shears, the desired length is secured.

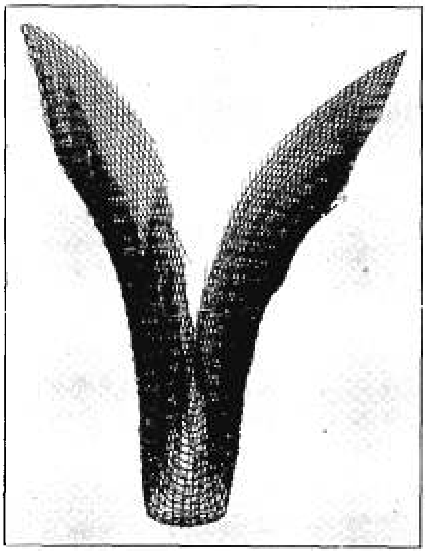

FIG. 1.—Splint for rabbit's leg—a simple and efficient device for maintaining immobilization of the fractured fragments, and one which will prevent the animal from gnawing its limb. This splint is made of copper wire mosquito-netting in the manner shown in Fig. 2. It is trimmed to the desired length and held in place by means of narrow strips of adhesive plaster.

After painting the line of sutures with $3\frac{1}{2}$ per cent. tr. iodin and application of the proper gauze dressing to the compound fracture, it was an easy matter to draw this *combination boot and splint* over the animal's leg and to fasten it with narrow strips of adhesive plaster (Fig. 1). Animals splinted in this manner were less able to injure their limbs or interfere with the progress of the experiment. The extreme simplicity of manufacture of such a device (as shown in Fig. 2), together with its minimal cost,[5] seemed to the author additional factors favoring its use.

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[5] Computed at the present wartime price of copper-wire mosquito-netting, at 12 cents per square foot, the actual cost of these rabbit splints is a cent and one-half apiece.

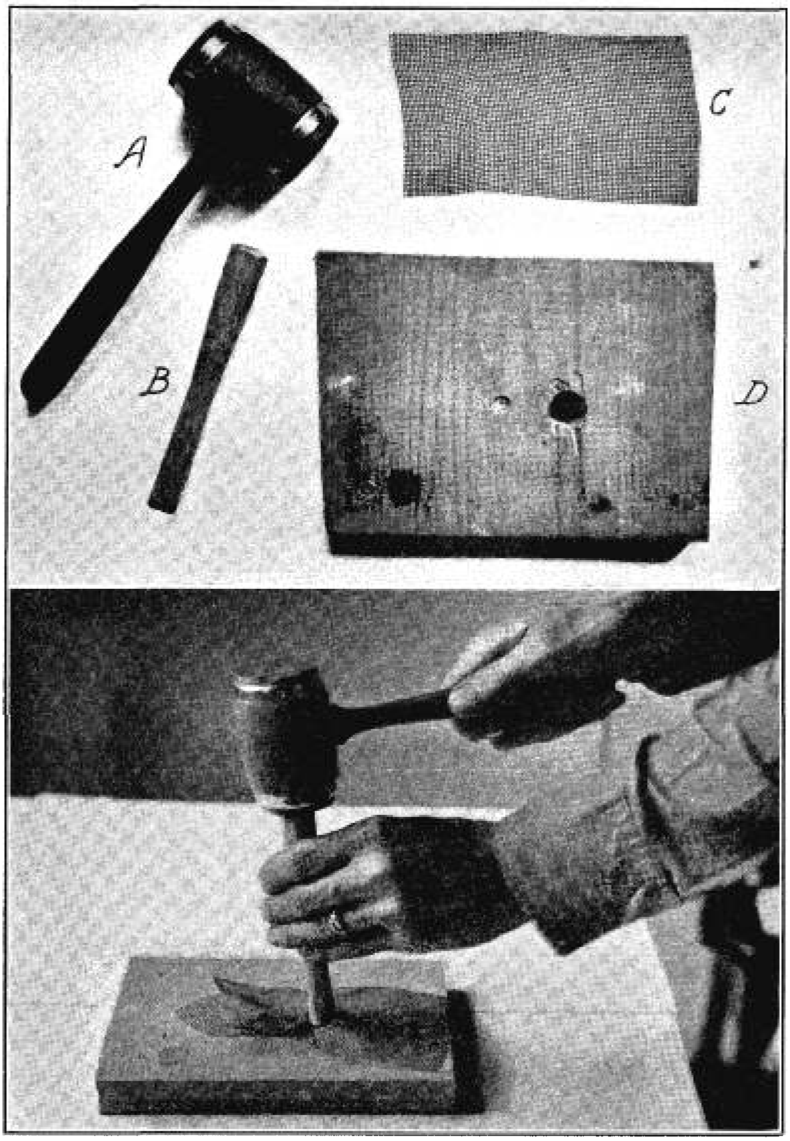

Fig. 2.—In the upper picture are shown the only materials required in the manufacture of the rabbit splint, illustrated in Fig. 1. These consist of a mallet, *A*; blunt soft pine plug, *B*; piece of copper wire mosquito-netting 3″ x 6″, *C*; and a pine board, *D*, which contains a hole ⅝ inch in diameter. The copper wire mosquito-netting is placed on the pine board, with its center directly over the hole. Through the hole, by means of the blunt plug, the netting is driven with a mallet and moulded into a cylinder, in the manner demonstrated in the lower photograph. The cost of these extremely simple, but efficient splints, is exactly a cent and one-half apiece.

In the later portion of our series of experiments relative to the etiology of pseudarthrosis, it was found possible to fracture, by open operation, only one of the two bones of the foreleg, the other bone serving as a splint. External splinting was, thereby, avoided. In these cases, it was our method, after careful approximation of the skin edges by interrupted linen sutures, to paint the line of suture well with 3½ per cent. tr. iodin, and to return the rabbit to its cage, without dressing or splint. Animals treated in this manner cared for themselves very well, and it was found that the wound healed quite as rapidly and without the occurrence of infection.

Our first animal experimentations at this hospital, numbering nearly a score, are included in this paper. These studies dealt with the roentgen ray, the removal of various amounts of bone and methods of splinting as possible causes of pseudarthrosis. Detailed reports of these experiments have been omitted, since, in every instance, the same result was obtained, namely, prompt union of the fractured fragments, usually with ample callus formation. Briefly summarized, our investigations and results were as follows:

(*a*) In one series of cases, sections of bone were removed from the radius, leaving a hiatus of considerable size, care being taken to remove *all* the small bone fragments. In every instance, prompt union by ample callus formation occurred.

(*b*) A second series of the same type of case as the foregoing, was then subjected to repeated long exposures to the roentgen ray; these cases likewise promptly united.

(*c*) A series of the same type was also splinted, as adequately as possible (see Fig. 1), and in other cases, no splint whatsoever was applied, the other bone of the foreleg being relied upon for support and to secure general alignment. Union in every case occurred promptly.

(*d*) In another series of cases, bone fragments were allowed to remain in the hiatus; as was anticipated, these cases showed a much more rapid bone growth than did those in which all the fragments were removed. Union occurred promptly, whether splinted or not, and whether or not subjected to massive and frequent exposures to the roentgen ray. Attention should be drawn to the clinical value of these observations which demonstrate the advantage of leaving *in situ*, whenever possible, attached fragments of bone in comminuted fracture, rather than removing them, as is frequently done by surgeons who do not grasp the fundamental laws of bone growth.

Following the suggested role of the roentgen ray as a possible factor in the etiology of pseudarthrosis, an experimental test of such a possibility was made on a series of cases. In each instance, after removal of ¼ inch of bone from the shaft of the right radius, the rabbit was subjected to massive roentgen-ray exposures at intervals of about five days, 5-inch gap, 3½ ampères, being used for five minutes. As controls, the left radii of the same animals were later treated in like manner, but without massive exposures to the roentgen ray. In the two groups of cases, no appreciable difference was found in the length of time required for union of the bones.

Illustrative of our attempts to produce pseudarthrosis by massive exposures to the roentgen ray, is Case No. 8, which, together with its control, is reported in detail, as follows:

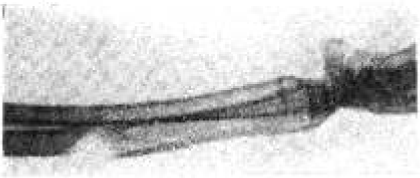

Fig. 3.—Case No. 8.—Second day after operation, showing gap in right radius from removal of ¼ inch of bone. This case was subjected to massive roentgen-ray exposures, 5-inch gap 3½ ampères being used for five minutes. This treatment was begun on the day after operation and continued for 4 successive intervals of about five days.

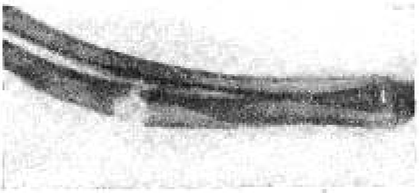

Fig. 4.—Case No. 8.—Twenty-five days after operation, showing evidence of a slight degree of bone growth. This radiograph was taken five days after the last of the series of massive roentgen-ray treatments.

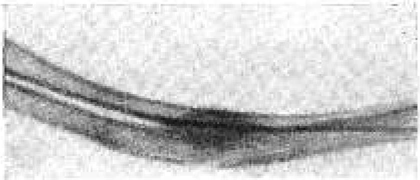

Fig. 5.—Case No. 8.—Forty-three days after operation, and about three weeks (twenty-three days) since last massive roentgen-ray treatment. Union is complete. Note that this radiograph shows more active bone growth and a more complete union than its control on which the roentgen ray was not used, save for short exposures in order to note progress of union.

Case No. 8.—Subject, common hare.

March 20, 1919. Fragment of bone, one-quarter inch in length, removed from shaft of right radius.

Exposures to roentgen ray.

March 21. Subjected to 5-inch gap, 3½ ampères, for five minutes.
March 25. Above treatment repeated.
March 30. Above treatment repeated.

April 4. Above treatment repeated.

April 9. Above treatment repeated.

Radiographic findings:

March 22. Second day after operation, roentgen ray shows gap of $\frac{1}{4}$ inch in shaft of radius. (See Fig. 3.)

April 14. Twenty-five days after operation. There is evidence of a slight degree of bone growth. (See Fig. 4.)

May 2. Forty-three days after operation—complete union is shown. (See Fig. 5.)

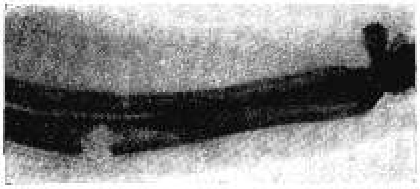

FIG. 6.—Case No. 8 *a*.—Control of Case No. 8. Second day after operation showing $\frac{1}{4}$ inch gap in left radius. This case was not subjected to massive roentgen-ray exposures.

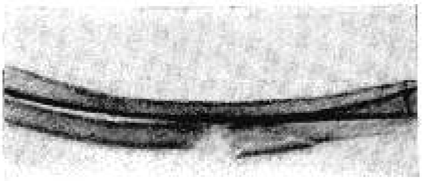

FIG. 7.—Case No. 8*a*.—Twenty-five days after operation. There is some evidence of bone proliferation.

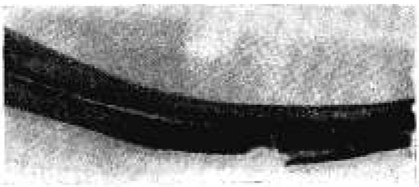

FIG. 8.—Case No. 8 *a*.—Forty days after operation, showing union of fragments. Compare with case No. 8, Fig. 5.

CASE No. 8*a*.—Control of Case No. 8.

A fragment of bone, one-quarter inch in length, was removed from the shaft of left radius.

Radiographic findings:

1. Second day after operation—roentgen rays shows gap of one-quarter inch in radius. (See Fig. 6.)
2. Twenty-five days after operation. There is evidence of a slight amount of bone proliferation. (See Fig. 7.)

3. Forty days after operation, union of fragments is shown. (See Fig. 8.)

In the foregoing experiments, it was found that bone growth was in no degree inhibited by the use of the roentgen ray. In fact, in Case No. 8, after a series of five massive exposures, complete union was shown forty-three days after operation, and proliferation even greater than occurred in its control on which the roentgen ray was not used, save for short exposures in the aim of obtaining radiographic findings. (See Figs. 5 and 8.)

It not infrequently results that a pure investigator, working along laboratory lines and not meeting clinical problems, goes far astray, and, in some instances, an excellent piece of research has come to naught owing to the fact that it was founded upon false premises. Illustrative of this is a report[6] of animal experimentation with fragmented bone grafts, recently published, in which that author introduces his paper with the following erroneous statement, as a premise:

"The bone (forearm) is too small to maintain a transplant in position by the use of a Lane plate or other device; and the insertion of an intramedullary splint with a dowel is a procedure of considerable difficulty and requires a large exposure of the fractured bone. In performing bone transplant operations in dogs while pursuing the study of bone repair, the writer was struck with the universally good results obtained by transplanting small bone fragments 1 to 2 mm. in size, to fill a defect in the shaft of the radius. Although this study is purely an experimental one, it is reasonable to assume from the results obtained that it will be of distinct clinical value in well selected cases."

The first statement, namely, that "the bone is too small to maintain a transplant in position by the use of a Lane plate or other device," is an unfortunate suggestion, since the Lane's plate should *never, under any circumstances,* be used as the fixative agent for the graft. The intramedullary splint, it is true, is not applicable in these cases; it is, however, an indisputable fact that the inlay graft, when properly inserted, affords an ideal fixation and an exceedingly promising prognosis. The most unfortunate part of that author's premise is his statement that, because by his method of placing small bone fragments in a hiatus freshly made in an animal's long bone, union was produced, it would be "reasonable to assume from results obtained that it would be of distinct *clinical* value in well selected cases,"[6] in the treatment of pseudarthrosis.

The error of such conclusions, as the foregoing, can be no better emphasized than by a summary of our results obtained with rabbits in our attempt to determine the cause of pseudarthrosis. In our experimentations, we failed absolutely to produce a single case of pseudarthrosis, simply because we were unable to prevent the early

[6] Bancroft, F. W.: The Use of Small Bone Transplants in Bridging a Bone Defect, Ann. Surg., 1918, lxvii. 457.

and rapid union of the fragments of the shafts of the long bones. In one series of our cases, discussed above (see *d.*), bone fragments were allowed to remain in the hiatus in precisely the same manner as described in the article quoted. Union in these cases, as has already been stated, occurred promptly whether the shaft fragments were splinted or not, and whether or not subjected to massive and frequent exposures to the roentgen ray. It is, thus, clear that the experimental findings, as set forth in the article above cited, can have no force, whatsoever, as argument for the *independent* use of osteoperiosteal grafts, in the clinical treatment of genuine pseudarthrosis, or malunion.

On the other hand, no one is more strongly convinced of the potency of fragmented, or osteoperiosteal, grafts as producive of bone growth, than the author, who, in experimental work as early as 1909 and 1910,[1] observed the unusual osteogenetic activity of such transplants. It is of interest, in this connection, to make reference to Case No. 5 (see Figs. 9 to 12), of our series of experimentations herewith reported. In this case, one slender fragment of bone was left in the hiatus formed by removal of about one-quarter inch of substance from the shaft of the radius. In striking contrast to those cases in which *all* particles of bone were removed from the gap at first operation (see Cases No. 8 and 8*a*, Figs. 3 to 8), this case showed a remarkable and rapid bone proliferation at the end of twenty days. Furthermore, by the thirty-first day, not only was there complete and solid union, but the gap was entirely filled with new bone. In cases in which all fragments were removed, a period of about forty-two days seemed required for union. The remarkable osteogenetic activity manifested in Case No. 5 was, of course, due to the presence of additional bone surfaces containing the potent bone-growing cells, namely, the fragment which originally remained, spanning the hiatus in the shaft of the radius. This bridge of bone functionated in the identical manner of an osteoperiosteal, or fragmented graft.

The value of the osteoperiosteal, or "sliver" graft, as a means of furnishing further foci for bone growth, has been repeatedly demonstrated, not only in the author's animal experimentations, but more particularly in the application of these grafts as supplements to the main fixation graft in his series of nearly 2000 cases of bone transplantation on the human subject. However, emphasis should be laid on the fact that in all clinical cases of pseudarthrosis, with or without loss of bone, such grafts should be employed *only as supplemental* to the main fixation graft which must be so inserted as to lie in generous contact with the primary source of blood supply and nourishment to bone, namely, the marrow cavity, or the cancellous bone structure. This can only be satisfactorily accomplished by the inlay method. The definite limitations to the use of fragmented, or osteoperiosteal, grafts have never been more convincingly demonstrated than by recent reports from American and European surgeons of the failure of these grafts, when used alone, to secure union in cases of pseudarthrosis.

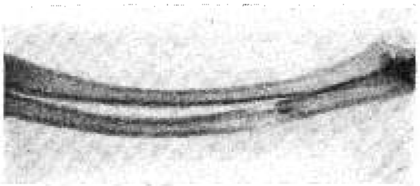

FIG. 9.—Case No. 5.—Five days after operation, showing the removal of about ¼ inch of the shaft of the radius. Note that in this case a slight bridge of bone has remained, spanning the gap between the shaft fragments.

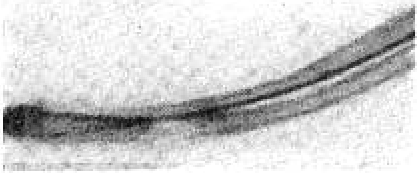

FIG. 10.—Case No. 5.—Twelve days after operation. There is slight evidence of bone growth. (In this figure the film was reversed in printing.)

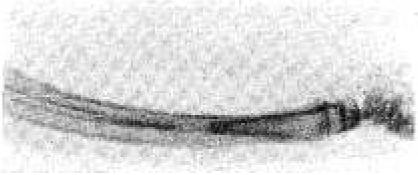

FIG. 11.—Case No. 5.—Twenty days after operation. Note the remarkable proliferation which has taken place. The original hiatus is nearly filled with new bone.

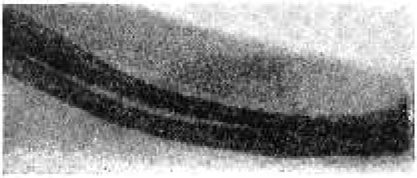

FIG. 12.—Case No. 5.—Thirty-one days after operation. The gap is completely filled with new bone and there is firm union. Compare the progress of bone growth in this case with that of case No. 8 (Figs. 3 to 5) and its control, case No. 8 *a* (Figs. 6 to 8). In both of these latter cases, there was complete removal of all fragments from the hiatus in the shaft of the radius. Note the striking contrast between these latter cases and case No. 5, in their respective radiographic findings. The remarkable osteogenetic activity demonstrated in Case No. 5 was due to the presence of the original bridge of bone left in the hiatus.

CONCLUSIONS.

1. In none of our experimentations with rabbits were we able to produce pseudarthrosis by repeated massive exposures to the roentgen ray, by removal of bone, nor by various degrees of splinting.

In every case, even when portions of the radius were removed to the extent of one-fourth of its entire length, we were prevented in our purpose by the early and rapid union of the shaft fragments, it being a well-known fact that bone growth in animals is much more rapid and constant than in the human subject.[7]

2. Frequent, massive exposures to the roentgen ray of fractures, with or without loss of bone, in no wise inhibited callus formation.

Following the suggestion that the common usage of the roentgen ray might play some role in the production of pseudarthrosis, series of fracture cases, with and without loss of bone, were subjected to long and repeated exposures. Comparison with a control group, on which the roentgen ray was not used, save for brief exposures incidental to observation of progress, showed that there was no difference in length of time required for the union of the bones in the two series of cases. Apparently the roentgen ray exerts no appreciable influence upon bone growth.

3. In cases of fracture, with loss of bone, in which *all* bone fragments were removed from the hiatus in the shaft of the radius, the average length of time for union was forty-two days.

Those cases of fracture in which the fragments were allowed to remain in the hiatus, showed a much more rapid and complete union, than occurred in the foregoing group. In one case of fracture, with loss of bone, in which one fragment was left bridging the gap, remarkable osteogenetic activity was manifest, complete restoration of continuity of the shaft occurring at the thirty-first day. This latter case affords a further demonstration of the value of the osteoperiosteal, or "sliver", graft, when used as a means of furnishing additional foci for bone growth.

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[7] In this connection, it is worthy of note that in many of the infected cases of fracture, with or without loss of bone, seen in the wards of this hospital, pseudarthrosis occurred, whereas, if the same relative amount of bone tissue be removed from a long bone of a rabbit, regeneration has been fairly rapid and complete.